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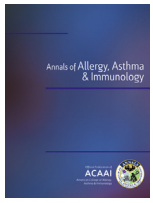

Perspective

When to suspect and work up allergic bronchopulmonary aspergillosis

Paul A. Greenberger, MD

Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

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Introduction

Because patients with undiagnosed and untreated allergic bronchopulmonary aspergillosis (ABPA) can develop recurrent pneumonias, bronchiectasis, chronic sputum production, loss of lung function, and ineffective control of asthma and respiratory failure, it is advisable to suspect ABPA so that an accurate diagnosis can be made and treatment plans can be recommended. Because of the emergence or progression of bronchiectasis, the failure to diagnose ABPA can result in preventable and irreversible lung damage, such as bronchiectasis and "honeycomb" pulmonary fibrosis for patients. The ideal approach is to diagnose ABPA before bronchiectasis or fibrotic changes have occurred. Infiltrates from ABPA can be relatively silent compared with the same amount of consolidation on chest radiograph that occurs with a bacterial community-acquired pneumonia. Furthermore, bronchiectasis may be extensive and not produce any sputum as illustrated in Figure 1 of a patient with long-standing ABPA.

Pathognomonic Findings

It is intuitively obvious that a disease should be suspected if there is a positive result on a pathognomonic test. The findings closest to pathognomonic tests for the diagnosis of ABPA in patients with asthma include (1) central bronchiectasis (inner half or two-thirds of lung fields on a high-resolution computed tomographic [CT] examination) primarily of the upper lobes and middle lobe, especially with mucous impaction,[1] and (2) the presence of highly opaque or hyperattenuated (hypercalcified or inspissated) mucous plugs.[2,3] The latter are more dense than paraspinal skeletal muscle and other parts of the mucous plug itself and have been reported to occur in 18% to 28% of patients with ABPA.[3,4] A pathognomonic constellation of findings should suggest ABPA when a patient with persistent asthma presents with a report of expectorating mucous plugs and is found to have developed pulmonary infiltrates in the upper lobe or middle lobe or perihilar mucous plugging, peripheral blood eosinophilia, total serum IgE level greater than 417 kU/L, and immediate skin test reactivity to *Aspergillus fumigatus*. Confirmation of ABPA in this setting can be the demonstration of elevated serum anti–*A fumigatus* IgE and or IgG antibodies compared with serum from *A fumigatus* skin test–positive patients with asthma who do not have sufficient criteria for a diagnosis of ABPA[5] or by the presence of central bronchiectasis on high-resolution CT examination of the lungs.[1,6] The response to initial therapy with prednisone should demonstrate clearing or a major decrease in the pulmonary infiltrates and a decrease in the total serum IgE of at least 33% by 6 weeks of treatment.[7] Such information helps support the diagnosis of ABPA as well.

When Classic Findings Are Not Present

In the absence of all of the classic findings and those that make up the diagnostic criteria[6,8] (Table 1), the steps in suspecting and working up ABPA can involve a high level of expertise for the integration of clinical information, laboratory tests, radiologic findings, skin test results, and sometimes histopathologic reports. ABPA should be considered when patients are found to have asthma and any other condition or finding, such as (1) bronchiectasis that is either noncystic fibrosis or cystic fibrosis in nature, (2) a history of prior pneumonias or lobar or lung collapse, (3) sputum plugs, (4) evidence of anti–*A fumigatus* IgE antibodies either by skin testing or in vitro immunoassay, (5) unexplained peripheral blood eosinophilia of 8% to 40%, (6) worsening severity of asthma, and (7) pathologic diagnoses of mucoid impaction of the bronchi, bronchocentric granulomatosis, or both. Although surgically performed lung biopsies are infrequent in patients who subsequently are diagnosed as having ABPA, it is notable that in patients with mucoid impaction from ABPA but not other causes, necrotic eosinophils and Charcot-Leyden crystals in the lumen are characteristic of allergic mucin.[9] It is thought that the presence of fungal hyphae in the mucin makes the diagnosis of ABPA certain.[9]

Of concern, oversights in critical thinking can occur when physicians and health care professionals use negative test results to exclude ABPA inappropriately. Some examples include (1) declaring

Reprints: Dr. Paul A. Greenberger, Northwestern University, Division of Allergy-Immunology, 676 N. St. Clair Street, #14018, Chicago, IL 60611; E-mail: p-greenberger@northwestern.edu.

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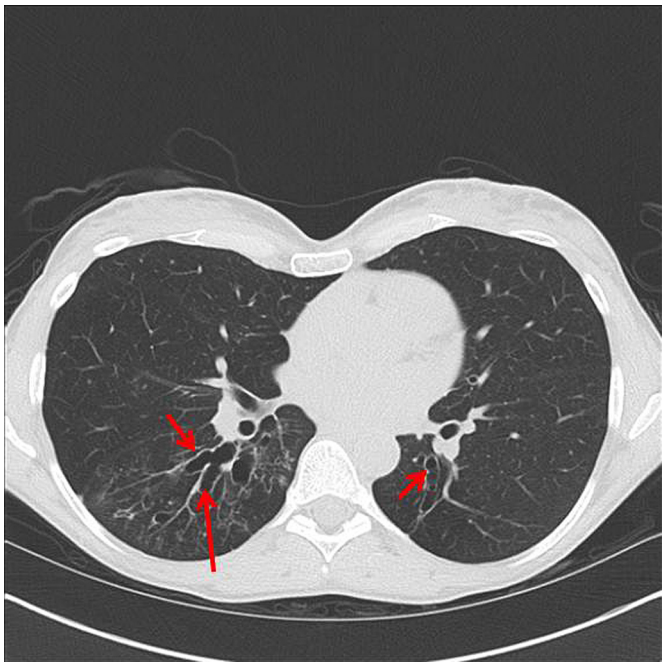

Figure 1. High-resolution computed tomographic examination of the lungs in a 50-year-old woman with long-standing allergic bronchopulmonary aspergillosis. The red arrows identify areas of bronchiectasis. The total IgE concentration was 304 kU/L, the anti–*Aspergillus fumigatus* IgE level was 3.49 kU/L (reference range, <2.0 kU/L), and the anti–*A fumigatus* IgG level was 4.98 kU/L (reference range, <2.0 kU/L).

that negative serum precipitating antibodies to *A fumigatus* exclude ABPA; (2) concluding that a negative result on skin prick testing with *A fumigatus* is as sensitive a screening test as both skin prick test and intradermal testing; (3) assuming that a total serum IgE level less than 417 kU/L (or <1000 kU/L) excludes ABPA when a patient is in the remission stage,[6] in the prednisone-dependent asthma stage,[6] or not having current pulmonary infiltrates; and (4) waiting for the presence of bronchiectasis to secure the diagnosis of ABPA, overlooking the diagnosis of seropositive ABPA.[10,11]

The diagnosis of ABPA may be considered provisional in some patients with asthma and a troubling cough or persistent wheeze that led to a chest radiograph demonstrating pulmonary infiltrates (eg, perihilar mucous plugging). The presence of peripheral blood eosinophilia of at least 8% might raise the possibility of ABPA so that a course of prednisone is administered. Additional workup can be performed, including, if it has not been performed, skin testing for *A fumigatus* (or potentially an in vitro immunoassay), total IgE concentration, culture of sputum if any is expectorated, and high-resolution CT of the lungs. The serum for total IgE concentration should be obtained as soon as possible to capture the peak (before prednisone) level.

Table 1
Diagnostic criteria for allergic bronchopulmonary aspergillosis[a]

Minimal diagnostic criteria[6]
1. Asthma
2. Immediate cutaneous reactivity to *Aspergillus fumigatus*
3. Elevated total IgE >417 kU/L
4. Elevated serum IgE and IgG to *A fumigatus* (twice controls of asthma)
5. Proximal (central) bronchiectasis on high-resolution computed tomographic examination (inner half to two-thirds of lung field)
Expert consensus minimal diagnostic criteria[8]
1. Asthma or cystic fibrosis with deterioration of lung function
2. Immediate *Aspergillus* species skin test reactivity
3. Total serum IgE ≥416 IU/mL (1,000 ng/mL or 416 kU/L)
4. Increased *Aspergillus* species–specific IgE and IgG antibodies
5. Chest radiographic infiltrates

[a]Criteria 1 through 4 are consistent with ABPA seropositive, whereas 1 through 5 are consistent with ABPA central bronchiectasis. It may be possible to diagnose ABPA central bronchiectasis with criteria 1 through 3 and 5 as truly minimal diagnostic criteria.

High Prevalence Settings for the Diagnosis of ABPA

The incidence and/or prevalence of ABPA has been reported to be 8% to 40% in specialized pulmonary clinics,[3,12] 28% in a referral allergy-immunology practice in Cleveland,[13] and 6% (3.6% with ABPA-central bronchiectasis and 2.4% with ABPA-seropositive) using data from 1983-1986 at the Northwestern University Allergy-Immunology Service in Chicago, Illinois.[14] With more recent data from 2000-2010 in which all new patients with asthma were skin prick tested and if the results were negative, intradermal testing to *A fumigatus*, 81 of 864 patients (9.4%) were diagnosed as having ABPA.[15] Because of the referral bias of patients to this author, data were categorized according to patients confirmed with ABPA by me (23.5%) or by my 5 colleagues (4.8%).[15] The diagnostic criteria[6] for ABPA included a total IgE level greater than 417 kU/L (equivalent to 417 IU/L or 1000 ng/mL), so we may have missed some patients with ABPA in remission or perhaps patients with persistent severe corticosteroid-dependent asthma whose total IgE at the time of presentation was not elevated. In all of these settings, the screening of patients included immediate skin testing with *A fumigatus.* The total serum IgE concentration was greater than 417 kU/L in 276 of 864 patients (31.9%) (with a positive immediate prick or intradermal skin test result to *A fumigatus*) from which 81 of 276 patients (29.3%) with an elevated total IgE concentration subsequently were diagnosed as having ABPA.[15] If the total IgE was greater than 417kU/L and there were elevated anti–*A fumigatus* IgE or IgG antibodies, high-resolution CT was performed to search for evidence of ABPA. Precipitating antibodies to *A fumigatus* were identified in just 42 of 81 patients with ABPA.

Although the differential diagnosis of pulmonary infiltrates with eosinophilia or pulmonary eosinophilia[16] is broad, McCarthy and Pepys[17] in London in 1971 reported that ABPA was present in 78% of patients with "pulmonary eosinophilia," meaning radiographic infiltrates and peripheral blood eosinophilia of at least 500/μL. Other examples include patients hospitalized with acute severe asthma (status asthmaticus), ambulatory patients with persistent severe asthma, and patients with hyper-IgE syndrome or chronic granulomatous disease.[18] I have observed ABPA in siblings (brother-sister)[19] and mother-daughter, and a family history of ABPA can suggest a prevalence as high as 4.9%.[20] ABPA can be diagnosed in 2% to 15% of patients with cystic fibrosis.[6,8]

The global prevalence of ABPA in adults with asthma recently has been estimated to be as high as 2.5%.[21] On a national or worldwide level, this number implies more patients with this potentially destructive lung disease.

Lower Prevalence Settings for the Diagnosis of ABPA

Although ABPA can be identified in patients with severe asthma, the diagnosis of severe asthma with fungal sensitization (SAFS) (Table 2)[22] implies that ABPA is not present. Nevertheless, there may be a continuum or overlap of severe asthma with skin test reactivity to *A fumigatus*,[23] SAFS, and ABPA. The inclusion criteria for SAFS consist of (1) high-dose inhaled corticosteroid (≥1,000 μg/d of beclomethasone dipropionate or its approximate equivalent of 500 μg/d of fluticasone propionate), (2) continuous oral corticosteroids (prednisolone, ≥5 mg for 6 months) or 4 to 6 courses of oral or intravenous corticosteroids in the past 12 to 24 months, (3) positive skin prick test result for fungi (but not necessarily to *Aspergillus* species) or *in vitro* demonstration of antifungal IgE (at least 0.4 kU/L), (4) total serum IgE concentration less than 1000 kU/L, and (5) absent precipitins to *Aspergillus*.[22] In a randomized controlled trial in patients with SAFS, itraconazole,

Table 2
Diagnostic criteria for severe asthma with fungal sensitization (SAFS)[22]

1. Severe asthma
2. Inhaled corticosteroid requirement: ≥1,000 μg/d of beclomethasone dipropionate or its approximate equivalent of 500 μg/d of fluticasone propionate
3. Continuous oral corticosteroids (≥5 mg of prednisolone for 6 months) or 4 to 6 courses of oral or intravenous corticosteroids in the past 12 to 24 months
4. Positive skin prick test result for fungi (but not necessarily to *Aspergillus* species) or in vitro demonstration of antifungal IgE of at least 0.4 kU/L
5. Total serum IgE concentration <1,000 kU/L
6. Absent precipitins to *Aspergillus*

Comments:

1. Patients with SAFS have severe asthma (criteria 1-3), whereas ABPA may occur in patients with persistent mild to severe asthma, occasional patients with intermittent asthma, and rarely patients without asthma.
2. Diagnosing a patient as having SAFS may allow for a trial of antifungal therapy. It remains to be determined whether the improvement in quality of life is because of potentiation of methylprednisolone by itraconazole with resultant greater corticosteroid effect or some other antifungal or anti-inflammatory effects of itraconazole.

200 mg twice daily for 32 weeks, was associated with improved asthma quality-of-life questionnaire scores.[22] There were insignificant changes in forced expiratory volume in 1 second.[22] Antifungal azoles offer a potential treatment approach for patients with SAFS. The number of patients who are found to convert from SAFS to ABPA or ABP mycosis is not known. ABPA should be suspected if new pulmonary infiltrates with peripheral blood eosinophilia occur and the total IgE concentration is now 417 kU/L or higher or has doubled over the initial concentration.

Some other low-risk settings for suspecting and then working up ABPA include (1) absence of asthma, although ABPA has rarely been described when such patients present with lobar collapse, (2) intermittent asthma, (3) persistent mild asthma, (4) asthma with atopic dermatitis, and (5) asthma, immediate skin test reactivity (prick or intradermal) to *A fumigatus,* and total serum IgE less than 417 kU/L. ABPA can be identified in some individual patients from each of these categories so their presence should not absolutely remove ABPA from the "suspicion" list. One area for suspecting or at least considering ABPA is in patients who present with pulmonary infiltrates and peripheral blood eosinophilia while receiving immunomodulatory therapy for rheumatoid arthritis (etanercept and tocilizumab).[24] In particular, a 68-year-old woman with rheumatoid arthritis receiving etanercept because infliximab had not been effective developed atelectasis of the middle lobe. She was reported to have no apparent asthma. The white blood cell count was 5,510/μL, with 12.2% eosinophils, and the total IgE concentration was 508 kU/L.[24] The anti-*Aspergillus* IgE was 22 kU/L.[24] When patients with asthma receive immunomodulatory therapies targeting tumor necrosis factor, or another critical cytokine or receptor, at least some degree of heightened suspicion should be entertained until the incidence of new-onset ABPA in this setting is clarified.

In the 1971 series of McCarthy and Pepys of 111 ABPA patients, 11 (10%) had nasal plugs with *A fumigatus* and eosinophils.[17] Occasional reports of concurrent allergic fungal (*Aspergillus*) rhinosinusitis and ABPA have appeared.[25]

Although the radiologic finding of "tree-in-bud" opacities occurs in ABPA from extensive mucous plugging of bronchioles (<2 mm in diameter), most patients with this finding do not have ABPA but can have other conditions, such as cystic fibrosis or infectious (mycobacterial, viral, bacterial) causes.[26]

Screening for *Aspergillus* Positive Asthma and ABPA

The evaluation of patients with persistent asthma should include an assessment for sensitization to fungi, including *A fumigatus,* and considering whether the patient is either in a higher or lower prevalence setting for undiagnosed ABPA. The severity and morbidity/mortality associated with fungal asthma have been described by various authors.[8,23,27-29] In planning to screen for fungal asthma and in particular ABPA, one first "casts a wide net" and then attempts to secure the diagnosis with confirmatory tests. Two steps in screening are discussed in the context of the clinical decision-making mnemonics SNOUT and SPIN. SNOUT means using a very *sensitive* test to rule *out* a diagnosis. If the highly sensitive test result is negative, then the condition likely is excluded (because there are few false-negative results). Applying SNOUT, one begins by skin testing patients with asthma (such as prick and intradermal if necessary) as a *highly sensitive* screening test for ABPA. If the skin test results are negative, then SNOUT applies, essentially ruling out the diagnosis of *A fumigatus* positive asthma or ABPA. SPIN implies using a very *specific* test to rule *in* a condition because there are few false-positive results. In a patient with a positive *A fumigatus* skin test result, steps toward confirmation of ABPA are untaken by using *highly specific* tests. If the results of confirmatory test results are positive, the diagnosis of ABPA is likely (SPIN). For example, the demonstration of elevated anti–*Aspergillus fumigatus* IgE and/or IgG antibodies[5] helps confirm ABPA in *A fumigatus*–positive patients with asthma. Alternatively, tests can be combined to confirm ABPA, an example of which is total serum IgE concentration greater than 417 kU/L *and* central bronchiectasis on high-resolution CT scanning.

Another approach in screening is to perform a prick skin test *and* determine the in vitro serum anti–*A fumigatus* IgE (>0.4 kU/L) for detection of fungal sensitization in patients with severe asthma.[29] However, concordance for positive results was just 54% for *A fumigatus* (and only 29% for *Penicillium chrysogenum*), meaning performing either test alone could have led to failing to identify evidence for the antifungal IgE, potentially falsely excluding fungal sensitization in severe asthma or ABPA.[29] One lesson from this study is that we need diagnostic tests or combination of tests with improved sensitivity, specificity, and positive and negative predictive values. For 40 years, it has been said that laboratory tests for many diseases and conditions would replace the clinician. Our patients will benefit if we work to stratify patients into high and low probabilities for ABPA and keep our clinical suspicion high for this uncommon but not rare condition. In addition, if ABPA is excluded, we must ensure that we are diagnosing and managing fungal asthma and its comorbidities with sufficient aggressiveness to maximize control yet minimize adverse effects from our treatments.

Practice Parameters and Expert Guidance

The Expert Panel Report 3 guidelines for the diagnosis and management of asthma recommended specialist referral to a "fellowship trained allergist or pulmonologist" under the category of identifying "comorbid conditions that may aggravate asthma."[30] Evidence A weighting was given for control of environmental factors and comorbid conditions that affect asthma, including "use skin testing or in vitro testing to reliably determine sensitivity to perennial indoor inhalant allergens to which the patient is exposed."[30] The practice parameter on allergy diagnostic testing of the American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology includes *A fumigatus* on its list of 36 "major clinically relevant aeroallergens of North America."[31]

Areas of Concern

There is disagreement over the diagnostic criteria of ABPA and approaches to treatment with oral steroids and antifungal medications. Subcutaneously administered allergen immunotherapy

with aqueous extracts of *A fumigatus* has not been studied formally, and such immunotherapy has not been proved to be helpful or harmful in ABPA. Modified (engineered) constructs of *A fumigatus*, such as Asp f 4, that were generated to delete most of the IgE-binding epitopes (but retain immunotherapeutic effects) have not been studied in clinical trials.[32] Successful[33,34] and unsuccessful[35] reports with omalizumab have been described, but a clinical trial in patients with ABPA and asthma would be more informative. We need research into novel immunomodulatory treatments that can improve the clinical course of ABPA. From a systems perspective, the possibility of ABPA in patients with asthma should be incorporated into improved pathways of care.

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